

CLAIMS

1. A dopaminergic neuron proliferative progenitor cell marker polynucleotide probe comprising a sequence selected from the following nucleotide sequences (1) to (5):

5 (1) a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NO: 1 or 2;

(2) a nucleotide sequence complementary to a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 3 or 4;

10 (3) a nucleotide sequence complementary to a nucleotide sequence encoding a sequence lacking a transmembrane domain in an amino acid sequence of SEQ ID NO: 3 or 4;

(4) a nucleotide sequence that hybridizes under stringent conditions with a polynucleotide consisting of a nucleotide sequence of SEQ ID NO: 1 or 2; and,

(5) a nucleotide sequence comprising at least 15 contiguous nucleotides selected from sequences of (1) to (4).

15 2. A method for selecting a dopaminergic neuron proliferative progenitor cell, wherein the method comprises the step of contacting the polynucleotide probe of claim 1 with a cell sample thought to comprise a dopaminergic neuron proliferative progenitor cell.

20 3. A method for selecting a dopaminergic neuron lineage cell, wherein the method comprises the steps of:

(1) selecting a dopaminergic neuron proliferative progenitor cell using the method of claim 2 for selecting the dopaminergic neuron proliferative progenitor cell;

(2) culturing the proliferative progenitor cell selected in step (1); and

25 (3) screening the cells cultured in step (2) by using a marker for a postmitotic dopaminergic neuron.

4. A dopaminergic neuron proliferative progenitor cell, which is selected by the method of claim 2.

30 5. A method for isolating a dopaminergic neuron proliferative progenitor cell-specific gene and a gene specific for each maturation stage from the proliferative progenitor cell to a dopaminergic neuron, wherein the method comprises the step of detecting and isolating a gene specifically expressed in the proliferative progenitor cell of claim 4 or a cell which is
35 differentiated, induced, or proliferated from the proliferative progenitor cell.

6. A method of screening for a compound which regulates proliferation and/or differentiation of a dopaminergic neuron lineage cell using maturation as an index, wherein the method comprises the steps of: contacting a test substance with the proliferative progenitor cell of claim 4 or a cell which is differentiated, induced, or proliferated from the proliferative progenitor cell; and detecting a change of the proliferative progenitor cell or the progenitor cell caused by the contact.
7. An antibody against a polypeptide selected from the following (1) to (6):
- (1) a polypeptide encoded by a polynucleotide consisting of a nucleotide sequence of SEQ ID NO: 1 or 2;
 - (2) a polypeptide comprising an amino acid sequence of SEQ ID NO: 3 or 4;
 - (3) a polypeptide comprising an amino acid sequence lacking a transmembrane domain in an amino acid sequence of SEQ ID NO: 3 or 4;
 - (4) a polypeptide comprising an amino acid sequence with a deletion, insertion, substitution, or addition of one or more amino acids in an amino acid sequence of SEQ ID NO: 3 or 4;
 - (5) a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions with a polynucleotide consisting of a sequence complementary to a nucleotide sequence of SEQ ID NO: 1 or 2; and,
 - (6) a polypeptide that is a fragment of a polypeptide of (1) to (5) comprising at least eight amino acid residues.
8. The antibody of claim 7, which is produced by the hybridoma FERM BP-10315 or FERM BP-10316.
9. A dopaminergic neuron progenitor cell marker antibody, which comprises the antibody of claim 7 or 8.
10. A method for selecting a dopaminergic neuron progenitor cell, wherein the method comprises the step of contacting the antibody of any one of claims 7 to 9 with a cell sample thought to comprise a dopaminergic neuron progenitor cell.
11. A method for selecting a dopaminergic neuron lineage cell, wherein the method comprises the steps of:
- (1) selecting a dopaminergic neuron proliferative progenitor cell using the method of claim 10
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- (2) culturing the progenitor cell selected in step (1); and
- (3) screening the progenitor cells cultured in step (2) by using a marker for a postmitotic dopaminergic neuron.

5 12. A dopaminergic neuron progenitor cell, which is selected by the method of claim 10.

13. A method for isolating a dopaminergic neuron progenitor cell-specific gene and a gene specific for each maturation stage from the progenitor cell to a dopaminergic neuron, wherein the method comprises the step of detecting and isolating a gene specifically expressed in the
10 progenitor cell of claim 12 or a cell which is differentiated, induced, or proliferated from the progenitor cell.

14. A method of screening for a compound which regulates proliferation and/or differentiation of a dopaminergic neuron lineage cell using maturation as an index, wherein
15 the method comprises the steps of: contacting a test substance with the progenitor cell of claim 12 or a cell which is differentiated, induced, or proliferated from the progenitor cell; and detecting a differentiated or proliferated progenitor cell caused by the contact.

15. A kit for treating Parkinson's disease, which comprises the dopaminergic neuron
20 proliferative progenitor cell of claim 4 or the dopaminergic neuron progenitor cell of claim 12.

16. A method for treating Parkinson's disease, wherein the method comprises the step of transplanting the dopaminergic neuron proliferative progenitor cell of claim 4 or the dopaminergic neuron progenitor cell of claim 12 into the brain of a patient.

25 17. A use of the dopaminergic neuron proliferative progenitor cell of claim 4 or the dopaminergic neuron progenitor cell of claim 12, for producing a kit for treating Parkinson's disease.

30 18. A method for detecting or selecting a dopaminergic neuron proliferative progenitor cell, which comprises the step of contacting a cell sample comprising the dopaminergic neuron proliferative progenitor cell with a second polynucleotide which hybridizes under stringent conditions with a first polynucleotide consisting of any one of:

- (1) the nucleotide sequence of SEQ ID NO: 1 or 2;
- 35 (2) a nucleotide sequence consisting of a polynucleotide encoding a polypeptide consisting of the amino acid sequence of SEQ ID NO: 3 or 4;

(3) a nucleotide sequence consisting of a polynucleotide encoding a polypeptide consisting of an amino acid sequence which lacks a transmembrane region in the amino acid sequence of SEQ ID NO: 3 or 4; and

5 (4) a nucleotide sequence consisting of a polynucleotide which hybridizes with a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1 or 2 under stringent conditions.

19. The method of claim 18, wherein the second polynucleotide comprises at least 15 nucleotides.

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20. A dopaminergic neuron proliferative progenitor cell population, which is selected by the method of claim 18 or 19.

21. A reagent for discriminating a dopaminergic neuron proliferative progenitor cell, which comprises a second polynucleotide as an active ingredient which hybridizes under stringent conditions with a first polynucleotide consisting of any one of:

- 15 (1) the nucleotide sequence of SEQ ID NO: 1 or 2;
- (2) a nucleotide sequence consisting of a polynucleotide encoding a polypeptide consisting of the amino acid sequence of SEQ ID NO: 3 or 4;
- 20 (3) a nucleotide sequence consisting of a polynucleotide encoding a polypeptide comprising an amino acid sequence which lacks a transmembrane region in the amino acid sequence of SEQ ID NO: 3 or 4; and
- (4) a nucleotide sequence consisting of a polynucleotide which hybridizes with a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1 or 2 under stringent conditions.
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22. The method of claim 21, wherein the second polynucleotide comprises at least 15 nucleotides.

30 23. A method for producing a postmitotic dopaminergic neuron precursor cell, wherein the method comprises the steps of:

- (1) selecting a dopaminergic neuron proliferative progenitor cell by the method of claim 18 or 19;
- (2) culturing the cell selected in step (1); and
- 35 (3) selecting the postmitotic dopaminergic neuron precursor cell from the cells cultured in step (2).

24. A method for producing a dopaminergic neuron, wherein the method comprises the steps of:

- (1) selecting a dopaminergic neuron proliferative progenitor cell by the method of claim 18 or 19; and
(2) culturing the cell selected in step (1).

25. The method of claim 24, further comprising the step of:

- (3) selecting a dopaminergic neuron from the cells cultured in step (2).

26. A method for detecting or selecting a dopaminergic neuron progenitor cell, which comprises the step of contacting a cell sample comprising the dopaminergic neuron progenitor cell with an antibody which is bound to a polypeptide consisting of the amino acid sequence of any one of:

- (1) the amino acid sequence of SEQ ID NO: 3 or 4;
(2) an amino acid sequence which lacks a transmembrane region in the amino acid sequence of SEQ ID NO: 3 or 4;
(3) an amino acid sequence mutated by one or more amino acid deletions, substitutions, or additions, or any combination thereof, in the amino acid sequence of SEQ ID NO: 3 or 4; and
(4) an amino acid sequence consisting of a polypeptide encoded by a polynucleotide which hybridizes under stringent conditions with a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NO: 1 or 2, or a partial sequence thereof.

27. The method of claim 26, wherein the polypeptide comprising the partial sequence comprises at least six consecutive amino acid residues.

28. A dopaminergic neuron progenitor cell population, which is selected by the method of claim 26 or 27.

29. The cell population of claim 28, which comprises 40% or more dopaminergic neuron progenitor cells in the entire cells.

30. A reagent for discriminating a dopaminergic neuron progenitor cell, which comprises an antibody as an active ingredient which is bound to a polypeptide consisting of the amino acid sequence of any one of:

- (1) the amino acid sequence of SEQ ID NO: 3 or 4;
- (2) an amino acid sequence which lacks a transmembrane region in the amino acid sequence of SEQ ID NO: 3 or 4;
- (3) an amino acid sequence mutated by one or more amino acid deletions, substitutions, or additions, or any combination thereof, in the amino acid sequence of SEQ ID NO: 3 or 4; and
- (4) an amino acid sequence consisting of a polypeptide encoded by a polynucleotide which hybridizes under stringent conditions with a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NO: 1 or 2, or a partial sequence thereof.

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31. The reagent of claim 30, wherein the polypeptide consisting of the partial sequence comprises at least six consecutive amino acid residues.

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32. The reagent of claim 30, wherein the antibody is produced by the hybridoma FERM BP-10315 or FERM BP-10316.

33. An antibody produced by the hybridoma FERM BP-10315 or FERM BP-10316.

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34. A method for producing a dopaminergic neuron proliferative progenitor cell, wherein the method comprises the steps of:

- (1) selecting a dopaminergic neuron progenitor cell by the method of claim 26 or 27; and
- (2) removing a postmitotic dopaminergic neuron precursor cell to select the dopaminergic neuron proliferative progenitor cell.

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35. A method for producing a postmitotic dopaminergic neuron precursor cell, wherein the method comprises the steps of:

- (1) selecting a dopaminergic neuron progenitor cell by the method of claim 26 or 27; and
- (2) culturing the cell selected in step (1).

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36. The method of claim 35, further comprising the step of:

- (3) selecting a postmitotic dopaminergic neuron precursor cell from the cells cultured in step (2).

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37. A method for producing a dopaminergic neuron, wherein the method comprises the steps of:

- (1) selecting a dopaminergic neuron progenitor cell by the method of claim 26 or 27; and

(2) culturing the cell selected in step (1).

38. The method of claim 37, further comprising the step of:

(3) selecting a dopaminergic neuron from the cells cultured in step (2).

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39. A kit for treating a neurodegenerative disease, which comprises at least one cell selected from the group consisting of:

(1) the dopaminergic neuron proliferative progenitor cell population of claim 20;

(2) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 23;

10 (3) a dopaminergic neuron produced by the method of claim 24;

(4) a dopaminergic neuron produced by the method of claim 25;

(5) the dopaminergic neuron progenitor cell population of claim 28;

(6) the dopaminergic neuron progenitor cell population of claim 29;

(7) a dopaminergic neuron proliferative progenitor cell produced by the method of claim 34;

15 (8) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 35;

(9) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 36;

(10) a dopaminergic neuron produced by the method of claim 37; and

(11) a dopaminergic neuron produced by the method of claim 38.

20 40. The kit of claim 39, wherein the neurodegenerative disease is Parkinson's disease.

41. A method for treating a neurodegenerative disease, which comprises the step of transplanting into the brain of a patient at least one cell selected from the group consisting of:

(1) the dopaminergic neuron proliferative progenitor cell population of claim 20;

25 (2) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 23;

(3) a dopaminergic neuron produced by the method of claim 24;

(4) a dopaminergic neuron produced by the method of claim 25;

(5) the dopaminergic neuron progenitor cell population of claim 28;

(6) the dopaminergic neuron progenitor cell population of claim 29;

30 (7) a dopaminergic neuron proliferative progenitor cell produced by the method of claim 34;

(8) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 35;

(9) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 36;

(10) a dopaminergic neuron produced by the method of claim 37; and

(11) a dopaminergic neuron produced by the method of claim 38.

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42. The method of claim 41, wherein the neurodegenerative disease is Parkinson's disease.

43. A use of at least one cell for producing a kit for treating a neurodegenerative disease, wherein the cell is selected from the group consisting of:

(1) the dopaminergic neuron proliferative progenitor cell population of claim 20;

5 (2) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 23;

(3) a dopaminergic neuron produced by the method of claim 24;

(4) a dopaminergic neuron produced by the method of claim 25;

(5) the dopaminergic neuron progenitor cell population of claim 28;

(6) the dopaminergic neuron progenitor cell population of claim 29;

10 (7) a dopaminergic neuron proliferative progenitor cell produced by the method of claim 34;

(8) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 35;

(9) a postmitotic dopaminergic neuron precursor cell produced by the method of claim 36;

(10) a dopaminergic neuron produced by the method of claim 37; and

(11) a dopaminergic neuron produced by the method of claim 38.

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44. The use of claim 43, wherein the neurodegenerative disease is Parkinson's disease.